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"COMPARATIVE CLINICAL TRIAL BETWEEN BRONCHOSCOPIC AND NON-BRONCHOSCOPIC BRONCHOALVEOLAR LAVAGE IN DIAGNOSIS OF VENTILATOR ASSOCIATED PNEUMONIA"

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ABSTRACT

Background

Our objective was to compare the results of bronchoscopic BAL and non-bronchoscopic BAL on diagnosis of ventilator-associated pneumonia (VAP).

Patients and Methods

The prospective comparative clinical trial was carried out in patients who were intubated for at least 48 hours. Every patient underwent both procedures, in a randomized fashion. The interpretation of cultures was done. 30 patients, who were intubated for 48 hours underwent both bronchoscopic and non-bronchoscopic bronchoalveolar lavage.

Results

From among the 30 patients, pathogen was isolated by bronchoscopic BAL in 29 patients, but only in 19 patients pathogen was isolated in non-bronchoscopic specimens. 10 patients had the same result both by bronchoscopy and non bronchoscopy. 8 patients had different pathogen isolation

Conclusions

Bronchoscopic BAL is a better and more accurate way to take samples from pulmonary secretion for diagnosis of VAP. Also, in patients with CPIS scores of less than 6, non-bronchoscopic BAL is not a reliable way for diagnosis of VAP.

KEYWORDS: Ventilator-Associated Pneumonia, Bronchoalveolar Lavage, Bronchoscopic Bronchoalveolar Lavage, Non Bronchoscopic Bronchoalveolar Lavage

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Original Article

INTRODUCTION

Ventilator-Associated Pneumonia

Ventilator-associated pneumonia (VAP), an important form of hospital acquired pneumonia (HAP), specifically refers top pneumonia developing in a mechanically ventilated patient more than 48 hours after tracheal intubation or tracheostomy. VAP continues to complicate the course of patients receiving mechanical ventilation in spite of major advances in techniques for its diagnosis and treatment [1, 2].

Epidemiology of VAP

Ventilator-associated pneumonia is the second most common nosocomial infection and the leading cause of death from nosocomial infections in critically ill patients. The incidence of VAP is age dependent, with 5 of every 1000

cases affecting hospitalized patients younger than 35 years of age, and up to 15 of 1000 in hospitalized patients, older than 65 years [3, 4].

The crude mortality from VAP may be as high as 30% to 70%, although several cofactors influence mortality during critical illness and make it extremely difficult to determine attributable mortality [5, 6].

CPIS Score

To start empiric antibiotic, there is an algorithm called The Clinical Pulmonary Infection Score (CPIS), which is based on five clinical assessments—temperature, blood leukocyte count, volume and purulence of tracheal secretions, oxygenation, pulmonary radiographic findings—each worth between 0 and 2 points table 1 [7] [8]. Moreover, a value of 6 was the threshold to accurately identify patients with pneumonia.

Table 1: Adapted from Pugin J, Auckentholer R, Mili N, et al. Diagnosis of Ventilator Associated Pneumonia by Bacteriologic Analysis of Bronchoscopic and Non-Bronchoscopic "Blind" Bronchoalveolar Lavage Fluid. Am Rev Respir Dis 1991; 143:1121-9

Criterion	*0*	*1*	*2*
Tracheal secretions	Absent	Not purulent	Abundant and purulent
Chest x-ray infiltrates	No	Diffuse	Localized
Temperature, °C	≥36.5 and ≤38.4	≥38.5 or ≤38.9	≥39 or ≤36
Leukocytes	≥4000 and ≤11000	<4000 or >11000	<4000 or >11000 + immature neutrophils >50% or >500
Pao_2/FIo_2	>240 or ARDS		≤240, no ARDS

Diagnostic Strategies for VAP

Detection of the causative organism is crucial for the diagnosis of VAP. The major difficulty of this approach is in obtaining samples from the lower respiratory tract, mainly because of its probable contamination with the upper airway flora, which may result in misinterpretation of cultures.

The diagnosis of VAP is problematic because there is no "gold standard" method for identifying parenchymal lung infections in ICU patients (other than Postmortem examination). As a result, the diagnostic approach to VAP is not standardized, and there are at least 6 different diagnostic methods to choose from (qualitative and quantitative cultures of tracheal aspirates, bronchial brushings with and without bronchoscopy, and bronchoalveolar lavage with and without a bronchoscopy) [9, 10].

Bronchoscopic BAL

It has been postulated that "invasive" diagnostic methods, including quantitative cultures of distal airway specimens obtained by using bronchoscopic bronchoalveolar lavage (BAL), bronchoscopic brush, protected BAL, or protected specimen brush (PSB), could improve identification of patients with true VAP and selection of appropriate antibiotics [11] [12] [13].

Non-bronchoscopic BAL

The introduction of non-bronchoscopic BAL has offered the ability to obtain lower respiratory samples without using a bronchoscope. A major advantage of non-bronchoscopic BAL is that, it can be performed by non physicians.

Patients and Methods

This prospective comparative clinical trial was conducted in the respiratory care unit (RCU) at the Hawler Teaching Hospital.

Including and Excluding Criteria

We enrolled 30 patients of age 16 years or more, who required ventilator support for the preceding 48 hours or more. Patients were excluded, if they had a contraindication for bronchoscope.

For each patient studied, the following parameters were recorded: Age, Gender, Primary diagnosis on admission, Indication of mechanical ventilation, Co morbid condition (COPD, Alcoholism, Cardiac disease, Neurological disease), GCS, Organ failure, Duration of ICU stay, Duration of mechanical ventilation, WBC count (4000-11000, <4000 or >11000, <4000 or >11000 with abnormal leukocyte), Temperature (36.5-38.4, 38.5-38.9, <36.5 or >39, Duration of fever), Radiologic pattern of chest X-ray (Focal, Diffuse, None), Tracheal secretion (Purulent secretion, Non purulent), PaO2/FiO2 ratio (<240, >240), Duration and type of Antibiotic received.

In each patient, two respiratory samples were collected, which included non-bronchoscopic BAL and bronchoscopic BAL. To avoid contamination of the lower airways, the non-bronchoscopic sampling was performed first.

Non-Bronchoscopic BAL Method

- Patient was sedated with 5-10 mg of midazolam.
- Ventilator setting was adjusted to increase tidal volume and oxygen fraction increased to 1. (100%)
- All the vital signs including heart rate, blood pressure and oxygen saturation were monitored during the entire procedure. The procedure was terminated if de-saturation occurred.
- We prepared necessary equipment prior to performing the procedure, which includes suction catheter, mucus trap, label mark, sterile saline, sterile drape, sterile gloves and vacuum.
- We put suction catheter and mucus trap in a sterile manner and lay on sterile drape, sterile gloves.
- Syringe with 20 ml sterile saline was prepared.
- Sterile suction catheter of size 14 Fr was inserted through the endotracheal tube, and blindly advanced into the distal airways till resistance is felt. The catheter was wedged in that position.
- Twenty milliliters of normal saline was instilled into the distal airway and aspirate was collected in a mucus trap. Procedure was repeated, if the aspirated fluid was less than 5 ml.
- We attached the appropriate patient label and marked as non-bronchoscopic BAL fluid. The sample was immediately transported for bacteriologic examination and quantitative cultures.

Bronchoscopic BAL Method

- After taking non-bronchoscopic sample, we waited for about 20 minutes to stabilize the patient.
- Again, patient was sedated with midazolam and ventilator support increased.
- Patient's vital signs were monitored.
- Necessary equipments were prepared including sterile drape, sterile gloves, 50 ml syringe with sterile saline, mucus trap, fiber optic bronchoscope and vacuum.
- Bronchoscope was introduced through endotracheal tube or tracheostomy and was positioned close to the orifice of the bronchus. The bronchopulmonary segment of interest, as determined by chest radiograph was selected. In patients with diffuse/bilateral lung infiltrates, bronchoscope was advanced into a bronchopulmonary segment of the right lower lobe for sampling.
- After introducing the bronchoscope and wedging the tip in the selected segmental or sub-segmental bronchus, 50 ml normal saline was instilled and gently aspirated to mucus trap.
- Procedure was repeated, if the aspirated fluid was less than 5 ml.
- Sample was labeled and marked as bronchoscopic BAL fluid. The sample was immediately transported for bacteriologic examination and quantitative cultures.

Statistical Analysis

Descriptive statistics were used, with all comparisons being paired, and all tests of significance two tailed. All values are expressed as the mean. Correlation coefficients were also calculated

RESULTS

A total of 30 ICU admitted cases have been included in this study.

- The data from Table 2 reveal that most of VAP patients had CPIS score of 0–5 representing approximately 57% of the total cases.
- The findings from Table 3 and 4 indicate that more than half of the patients had non-purulent tracheal discharge with diffuse radiological pattern on chest X- rays.
- The findings from Table 5 indicate that there was a significant statistical association between the type of tracheal secretions and the radiological patterns. Patients with purulent tracheal discharge showed a diffuse pattern on chest X – rays, while those who did not have any secretions did not show any radiological abnormalities.
- The data of Table 6 reveal that the most frequent antibiotics used before taking the samples and sending for culture and sensitivity were: Meropenem (for seven cases) followed by Ceftriaxone (for 6 cases) then Imepenim (for five patients). Together, the three antibiotic agents accounted for 60% of all antimicrobial drugs that have been used to treat admitted patients in ICU empirically, prior to performing swab taking and waiting for results of laboratory culture and sensitivity tests.
- The data of Table 7 indicate that in most of the conditions; antibiotics were used empirically and on clinical

evaluation showed more than 60% resistance after results of laboratory culture and sensitivity, except Cefepim, for which no resistance, and Levofloxacillin, for which only one third resistances have been recorded. On the other hand, those who received Ampiclox showed 100% resistance to it, according to laboratory result.

- The findings of Table 8 indicate that different microorganism have been isolated 29 times by BAL method; *serratiamarcescens* being most frequently isolated organism followed by *pseudomonas aeruginosa* in reverse to non-bronchoscopic BAL procedure by which, bacteria have been isolated only on 19 occasions. *Pseudomonas aeruginosa* and *E. Coil* were mainly isolated.
- The finding from Table 9 shows that the vast majority of bacteria were of Gram negative type; constituting 84 – 89% of all cases.
- The data of Table 13 indicate that in both procedures; BAL and NBAL, ampicillin reported the highest resistance rate which was close to 90%. Three antibiotics (amikacin, levofloxacillin and ciprofloxacillin) showed the least resistance of only 41% by using BAL method. In contrary, two antibiotics revealed a low resistance rate of 42% by using NBAL procedure; namely: cefoxitin and ceftazidime.

Table 2: CPIS Score of Patients

CPIS	Number	Percent
0 – 5	17	56.6%
≥ 6	13	43.4%
Total	**30**	**100%**

Table 3: Radiological Pattern

Radiologic Pattern	Frequency	Percent
Focal	5	16.7%
Diffuse	16	53.3%
None	9	30%
Total	**30**	**100%**

Table 4: Tracheal Secretion of Patients

Tracheal Secretion	Frequency	Percent
Purulent	11	36.7
Non purulent	17	56.7
None	2	6.7
Total	**30**	**100.0**

Table 5: Association between Radiological Patterns and Tracheal Secretion

Radiologic Patterns		Tracheal Secretions			Total	P – value
		Purulent	Non-Purulent	None		
Focal	Number	3	2	0	5	0.03
	% within Tracheal secretion	27.3%	11.8%	0.0%	16.7%	
Diffuse	Number	8	8	0	16	
	% within Tracheal secretion	72.7%	47.1%	0.0%	53.3%	
None	Number	0	7	2	9	
	% within Tracheal secretion	0.0%	41.2%	100.0%	30.0%	
Total	**Number**	**11**	**17**	**2**	**30**	
	% within Tracheal Secretion	**100%**	**100%**	**100%**	**100%**	

Table 6: Types of Received Antibiotics Prior to Taking Samples

Antibiotics	Frequency	Percent
Cefepim	1	3.3
Ampiclox	2	6.7
Cefotaxim	3	10.0
Levofloxacillin	3	10.0
Amoxiclave	3	10.0
Imepenim	5	16.7
Ceftriaxone	6	20.0
Meropenem	7	23.3
Total	**30**	**100.0**

Table 7: Antibiotics Patients Received and Showed Resistance on Lab Results

Type of Antibiotic	Resistant Antibiotic	No. of Patients Received	Percentage
Imepenim	3	5	60%
Meropenem	4	7	57%
Ceftriaxone	4	6	66%
Cefotaxim	2	3	66%
Cefepim	0	1	0
Levofloxacillin	1	3	33%
Ampiclox	2	2	100%
Amoxiclave	2	3	66%
Average	**18**	**30**	**60%**

Table 8: Microorganisms Isolated by Different Procedures

Organism	Bronchoscopic	Percentage	Non Bronchoscopic	Percentage
Acinetobacterbaumani	4	13%	4	21%
Serratiamarcescens	8	27%	3	17%
Staphylococcus aureus	3	11%	0	0
Escherichia coli	4	13%	4	21%
Pseudomonas aeruginosa	6	21%	4	21%
Stenotrophomonasmaltophilia	1	4%	1	5%
Klebsiella pneumonia	3	11%	0	0
Staphylococcus lentus	0	0	2	10%
Staphylococcus intermedius	0	0	1	5%
Total	**29**	**100%**	**19**	**100%**

Table 9: Results According to GRAM Stain

Gram Stain	BAL	Percentage	NBAL	Percentage
Gram positive	3	11%	3	16%
Gram negative	26	89%	16	84%
Total	**29**	**100%**	**19**	**100%**

Table 10: Differences in Results of Bronchoscopic and Non Bronchoscopic BAL

Situations	No. of Patients
Same organism isolated (+ &+)	10
Different organism isolated (+&+)	8
+ve in bronchoscopic and –ve in non bronchoscopic	11
-ve in bronchoscopic and +ve in non bronchoscopic	1
-ve in both bronchoscopic and non bronchoscopic	0
Total	**30**

Table 11: Results According to CPIS Score (Bronchoscopic)

	0-5	Percentage	>6	Percentage
Bronchoscopic BAL (+ve for organism)	16	94%	13	100%
Bronchoscopic BAL (-ve for organism)	1	6%	0	0
Total	**17**	**100%**	**13**	**100%**

Table 12: Results According to CPIS Score (Non-Bronchoscopic)

	0-5	Percentage	>6	Percentage
Non-bronchoscopic BAL (+ve for organism)	8	47%	11	85%
Non-bronchoscopic BAL (-ve for organism)	9	53%	2	15%
Total	**17**	**100%**	**13**	**100%**

Table 13: Resistance of Organisms to Antibiotics

Type	BAL	Percentage	NBAL	Percentage
Ampicillin	27	93%	17	89%
Amoxicillin	24	82%	16	84%
Amoxiclave	24	82%	16	84%
Piperacillin	21	72%	11	57%
Cefazolin	25	86%	14	73%
Cefoxitin	18	62%	8	42%
Ceftazidime	19	65%	8	42%
Ceftriaxone	25	86%	16	84%
Cefepim	21	72%	9	47%
Cefatoxim	25	86%	15	78%
Imepenim	13	44%	10	52%
Meropenem	14	48%	10	52%
Amikacin	12	41%	11	57%
Gentamicin	18	62%	9	47%
Tobramicin	19	65%	11	57%
Ciprofloxacillin	12	41%	9	47%
Levofloxacillin	12	41%	9	47%
Nitrofurantoin	23	79%	14	73%
Trimethoprim	20	68%	9	47%
Total No of Organisms	**29**		**19**	

DISCUSSIONS

Ventilator-associated pneumonia (VAP), an important form of hospital acquired pneumonia (HAP), continues to complicate the course of patients receiving mechanical ventilation in spite of major advances in techniques for its diagnosis and treatment. It is a major medical problem and is associated with longer stay in the Intensive Care Unit (ICU) and in the hospital, high cost, and high mortality rates.

Over diagnosis of VAP have serious potential consequences, including exposing critically ill patients to unnecessary antibiotics. However, withholding antibiotic treatment from patients who actually do have VAP may result in a protracted illness, increased duration of ventilation and ICU stay, and possibly death.

Table 5 shows that there was statistically significant relation between the presence of tracheal secretion and radiological pattern. Patients with purulent tracheal discharge showed a diffuse pattern on chest X – rays, while those who did not have any secretions did not show any radiological abnormalities.

In our study, all of the patients were receiving antibiotics before taking samples, either because of primary conditions or in the management of VAP. Most of our patients received carbapenem and third generation cephalosporin, which accounts for about 75% of all cases. The data of table 7 indicate that most of antibiotics that were empirically given showed resistant after results of the laboratory came (an average of 60%). For Cefepim, no resistance and for Levofloxacillin only one third resistance has been recorded. On the other hand, those who received Ampiclox showed 100% resistance to it, according to laboratory results.

Table 13 showed that microorganism that is cultured had a high percentage of resistance to antibiotics, which we commonly use in the management of VAP. Most of microorganism was resistant to penicillin and cephalosporin groups, mainly because they are widely used in the management of various infections. On the other hand, they had less resistance to macrolide and carbamapenem groups.

Different microorganisms were isolated in culturing of BAL samples which are mainly Gram negative both by bronchoscopic and non bronchoscopic (table 8 and 9). According to our results, more than 80% of microorganisms isolated were gram negative. This may be due to duration of mechanical ventilation of longer than 7 days before onset of VAP, prior antibiotic use, and prior use of broad-spectrum drugs (third-generation cephalosporin, fluoroquinolones, and/or carbapenem) [16].

Pathogens that were isolated include *Acinetobacterbaumani* (13%), *Serratiamarcescens* (27%), *Staphylococcus aureus* (11%), *Escherichia coli* (13%), *Pseudomonas aeruginosa* (21%), *Stenotrophomonasmaltophilia* (4%) and *Klebsiella pneumonia* (11%) by bronchoscopy; and *Acinetobacterbaumani* (21%), *Serratiamarcescens* (17%), *Escherichia coli* (21%), *Pseudomonas aeruginosa* (21%), *Stenotrophomonasmaltophilia* (5%), *Staphylococcus lentus* (10%) and *Staphylococcus intermedius* (5%) by non bronchoscopy.

Few studies have assessed whether the pathogens that cause pneumonia in ventilated patients differ from those in patients who are not mechanically ventilated. Weber et al. [17] evaluated patients admitted to a single center over a 4-year period and identified 327 episodes of VAP and 261 episodes of nosocomial pneumonia. The infecting flora in ventilated patients mostly included gram-negative bacilli such as *P. aeruginosa* (59.0%), *Stenotrophomonasmaltophilia* (17.50%), and *Acinetobacter*species (6.75%), while a lower incidence of nosocomial pneumonia due to *P. aeruginosa*, *Acinetobacter* spp., and *S. maltophilia* was found.

We took samples from 4 patients in the same day, when results of culture came. *Acinetobacterbaumani* were isolated which shows an outbreak in ICU and are usually associated with colonized respiratory support equipments or fluid from incomplete disinfection of ventilator equipment [18].

In one occasion, *Stenotrophomonasmaltophilia* was isolated which frequently colonizes breathing tubes such as endotracheal or tracheostomy tubes, the respiratory tract and indwelling urinary catheters. Infection is usually facilitated by the presence of prosthetic material (plastic or metal), and the most effective treatment is removal of the prosthetic material [19].

In our study; bronchoscopic BAL samples for 29 patients were positive and at least one pathogen were isolated on culture and only in one patient, no pathogen was grown. On the other hand, in 19 patients; non bronchoscopic BAL samples were positive and in 11 patients no microorganism was isolated. In a study by A. Leo and colleagues, they took samples from 25 patients both by bronchoscopy and non-bronchoscopy. Only two patients had discordant results [20].

The high rate of polymicrobial infection in VAP has been shown repeatedly. Combes and colleagues [22] studied 124 ICU patients, of whom 65 (52%) had monomicrobial VAP and 59 had (48%) polymicrobial VAP. In most patients, two different bacteria were isolated (42 patients, 34%). In our study in 8 patients (26%), two pathogens were isolated.

According to table (11 and 12) non-bronchoscopic samples from patients with CPIS score of more than 6 were mostly positive (about 85% of samples), while they were mainly negative in patients with CPIS score of less than 6 (about 53%). From this, it can be concluded that in patients with CPIS score of less than 6, bronchoscopic sampling is a better choice.

CONCLUSIONS

- The diagnosis of VAP is problematic, because, there is no "gold Standard" method for identifying parenchymal lung infections in ICU patients. We tried to compare results of bronchoscopic and non-bronchoscopic bronchoalveolar lavage in this study.
- In this study, most of the antibiotics that were empirically given showed resistannce after results of laboratory came (an average of 60%). Also, microorganisms that were isolated were mainly resistant to penicillin and cephalosporin group.
- According to our results, more than 80% of microorganisms isolated were gram negative. Pathogens that were mostly isolated include *Serratiamarcescens*, *Escherichia coli* and *Pseudomonas aeruginosa*.
- In this study; bronchoscopic BAL samples for 29 patients were positive and at least one pathogen were isolated on culture, and, only in one patient no pathogen was grown.
- On the other hand, in 19 patients; non-bronchoscopic BAL samples were positive and in 11 patients no microorganism was isolated. In10 patients, the same microorganisms have been grown by bronchoscopy and non-bronchoscopic BAL, which accounts for 33% of all our cases, but in eight patients different bacteria isolated.
- Over 11 instances the organisms were positive on bronchoscopic BAL, while they tested negative on non-bronchoscopic BAL, the reverse happened only once.
- So, we can conclude that bronchoscopic BAL is better and more accurate way to take samples from pulmonary secretion for diagnosing of VAP.
- Also we can conclude that in patient with CPIS score of less than 6, non-bronchoscopic BAL is not a reliable way for diagnosing of VAP.

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